FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	PU3556USW
	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR) 09/830037

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB99/03472	20 October 1999	22 October 1998

TITLE OF INVENTION
FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

APPLICANT(S) FOR DO/EO/US
Gordon J. DOW; Keith Arthur JOHNSON; Frances Furr KELLY; Robert William LATHROP; Rukmini RAJAGOPALAN

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31)
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau)
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau)
   b ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired
   d. ☒ have not been made and will not be made
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5))
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409)
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included
15. ☒ A **FIRST** preliminary amendment
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4)
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Copy of PCT Request (Form PCT/RO/101)
Copy of PCT Publication cover
Copy of Correction to PCT Request before 30th Month

U.S. APPLICATIONNO.(IFKNOWN,SEE37CFR	INTERNATIONALAPPLICATIONNO.	ATTORNEY'SDOCKETNUMBER
09/830037	PCT/GB99/03472	PU3556USW

24. The following fees are submitted:.	CALCULATIONS	PTOUSEONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1000.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$860.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1 445(a)(2)) paid to USPTO	$710.00	
☐ International preliminary examination fee (37 CFR 1 482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$690.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$0.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	24 - 20 =	4	x $18.00	$72.00	
Independent claims	4 - 3 =	1	x $80.00	$80.00	
Multiple Dependent Claims **(check if applicable)**			☐	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$1,012.00	
☐ Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				$0.00	
SUBTOTAL =				$1,012.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	$0.00	
TOTAL NATIONAL FEE =				$1,012.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	$0.00	
TOTAL FEES ENCLOSED =				$1,012.00	
			Amount to be: refunded		$
			charged		$

a. ☐ A check in the amount of _____ to cover the above fees is enclosed

b. ☒ Please charge my Deposit Account No. **07-1392** in the amount of **$1,012.00** to cover the above fees. A duplicate copy of this sheet is enclosed

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **07-1392** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

David J. Levy, VP
GlaxoSmithKline
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Five Moore Drive, PO Box 13398
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SIGNATURE

James P. RIEK
NAME

39,009
REGISTRATION NUMBER

April 20 2001
DATE

Express Mail Label
EL395942518US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gordon J. DOW, et al
International Application No.: PCT/GB99/03472
International Filing Date: 20 October 1999
Title: FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

Commissioner of Patents
Washington, D.C. 20231

FIRST PRELIMINARY AMENDMENT

Dear Sir:

The above identified application is being transmitted herewith for entry in the US National Phase under Chapter II of the PCT for the purpose of adding the priority information. Please amend the application as follows:

In the Abstract:

Please substitute the attached Abstract, which has been placed on a separate sheet of paper according to US practice, as required under 37 CFR 1.72(b)

In the Specification:

On the first line of the specification, after the Title, please add:

--This application is filed pursuant to 35 U.S.C. §371 as a United States National Phase Application of International Application No. **PCT/GB99/03472** filed **20 October 1999**, which claims priority from **GB9823036.0 filed 22 October 1998**.--

REMARKS

Applicants have attached an abstract on a separate sheet of paper as required by US practice. Applicants have amended the specification for purposes of adding the priority information. It is respectfully submitted that

the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted;

James P. RIEK, 2nd April 2001
Attorney of Record, Reg. No. 39,009
GlaxoSmithKline
Corporate Intellectual Property Department
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FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

ABSTRACT

A fluticasone lotion having improved vasoconstrictor and anti-inflammatory activity and higher than expected potency. The fluticasone lotion contains 0.05 weight percent fluticasone propionate and an oil-in-water vehicle that includes excipients. The fluticasone lotion is unexpectedly efficacious while exhibiting an improved safety profile.

Via Facsimile

TO: PCT Examination International Bureau of WIPO 34 Chimin des Colombettes 1211 Geneva 20 Switzerland Fax: 011 41 22 740 1435	**Correction to PCT Request before 30th Month**
Applicant's File Reference **PU3556WO**	Applicant **Glaxo Group Limited**
International Application No. **PCT/GB99/03472**	International Filing Date: **20 October 1999**
30th Month Deadline: **22 April 2001**	Title: **Fluticasone Lotion Having Improved Vasoconstrictor Activity**

Correction:

Please make the following correction to PCT Request PCT/GB99/03472 filed on 20 October 1999.

-Please change address of inventors/applicants: Keith Arthur JOHNSON; Frances Furr KELLY; Robert William LATHROP and Rukmini RAJAGOPALAN to:

GlaxoSmithKline
c/o Corporate Intellectual Property Department
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Please acknowledge receipt of this request by return fax to (919) 483-7988 in the United States. If there should be questions, please call (919) 483-2252.

Thank you.

Sincerely,

30 Mar 01

Christopher P. Rogers
Attorney for Applicant

Express Mail Label
EL395942518US

FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

FIELD OF THE INVENTION

The present invention is generally directed to a lotion comprising fluticasone.

BACKGROUND OF THE INVENTION

Fluticasone propionate is a steroid having anti-inflammatory, anti-pruitic, and vasoconstrictive properties. Fluticasone propionate cream (0.05%) is sold under the tradename CUTIVATE® cream. Each gram of CUTIVATE® cream (0.05%) contains 0.5 mg fluticasone propionate in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, buffers and preservatives.

Mineral oil is a known occlusive agent. Occlusion in topical drug delivery is known to increase the vasoconstrictor potency of the topical steroid. By increasing the vasoconstrictor potency, the effectiveness of the steroid is increased. However, occlusive agents such as mineral oil can reduce the aesthetic appeal of topical formulations as they may impart an undesirable oily feel to the skin. By removing or significantly reducing the concentration of the occlusive agent, a decrease in the vasoconstrictor potency of the steroid would be expected. Thus, the effectiveness of the topical steroid formulation would be decreased.

The present fluticasone lotion invention unexpectedly shows increased vasoconstrictor potency of fluticasone at decreased concentrations of occlusive agent, thus increasing the steroid effectiveness. The instant fluticasone lotion also significantly improves the organoleptic feel and spreadability of the drug over a large area as compared to a cream. Specifically, the instant fluticasone lotion has improved vasoconstrictor activity over fluticasone cream formulations. The fluticasone lotion is systemically safe and exhibits significant vasoconstrictor potency and efficacy and excellent anti-inflammatory activity.

SUMMARY OF THE INVENTION

One aspect of the invention is a topical lotion comprising about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; a thickening effective concentration of at least one thickener; a conditioning effective concentration of at least one skin conditioning agent; and, an emulsifying effective amount of a surfactant. Unless indicated otherwise herein, all percentages are in terms of weight percent (i.e., w/w, wt.%, etc.). Unless indicated otherwise herein, the term "about" is intended to include values, e.g., weight percents, proximate to the recited range that are equivalent in terms of the functionality of the individual ingredient, the composition or the invention. In addition, unless indicated otherwise herein, a recited range (e.g., weight percents or carbon groups) includes each specific value or identity within the range.

Another aspect of the present invention is a topical fluticasone lotion for the treatment of skin conditions (i.e., dermatological disorders). The lotion comprises about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt.% of a C_{14}-C_{20} fatty alcohol, or mixtures thereof; about 1.0 to 5.0 wt.% of at least one skin conditioning agent; about 5.0 to 15.0 wt.% of propylene glycol; up to about 10.0 wt.% mineral oil or soft white paraffin, and the balance being water. The lotion optionally contains additives such as preservatives and buffers.

Another aspect of the invention is a topical fluticasone lotion comprising fluticasone propionate in an amount of from about 0.005 to 1.0 wt.%; a C_{14}- C_{20} fatty alcohol, or mixtures thereof, in an amount of from about 3.0 to 7.0 wt.%; at least one skin conditioning agent in an amount of from about 0.5 to 3.0 wt.%; at least one surfactant in an amount of about 0.25 to 3.0 wt.%; propylene glycol in an amount of from about 7.0 to 12.0 wt.%; up to about 10 wt.% mineral oil or soft white paraffin; and the balance in water, preferably purified water, USP.

Yet another aspect of the invention is a method of treating a skin condition. A skin condition (or dermatological disorder) includes, but is not limited to, corticosteroid-responsive dermatosis, atropic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting and pruritis. The method comprises the

steps or acts of providing a lotion including about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt.% of a C_{14}-C_{20} fatty alcohol or mixtures thereof; about 1.0 to 5.0 wt.% of one or more skin conditioning agents; about 5.0 to 15.0 wt.% of propylene glycol; up to about 10.0 wt.% of mineral oil or white soft paraffin, and the balance in purified water; and, applying the lotion to the skin having the skin condition. Preferably, the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5. The lotion of the present invention has the added benefit of being chemically and physically stable for at least 6 months at 40°C.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Fluticasone or a pharmaceutically acceptable salt or ester thereof, preferably fluticasone proprionate, is present in the formulation in a concentration of from about 0.005 to 1.0 wt.% preferably 0.005 to 0.5 wt.%, and more preferably about 0.005 to about 0.1 wt.%. The C_{14}-C_{20} fatty alcohol or mixtures thereof are present in the formulation as a thickener and/or stabilizer. Examples include, but are not limited to, cetyl alcohol, stearyl alcohol, and cetostearyl alcohol. The C_{14}-C_{20} fatty alcohol is present in a concentration in the range of from about 1.0 to 10.0 wt.%, preferably about 3.0 to 7.0 wt.%, and more preferably about 4.0 to 6.0 wt.%.

Conventional skin conditioning agents, such as emollient skin conditioning agents, may be present in the lotion of the present invention. Skin conditioning agents are defined in the CTFA (Cosmetic Toiletry and Fragrance Association) Cosmetic Ingredient Handbook (2nd ed. 1992) and the Handbook of Pharmaceutical Excipients (2nd ed. 1994). Preferred examples of such skin conditioning agents include, but are not limited to, cholesterol, glycerine, glycerol monostearate, isopropyl myristate and palmitate, and lanolin alcohols, or mixtures thereof. Particular examples are isopropyl myristate and cetostearyl alcohol. The skin conditioning agent is present in a concentration in the range of from about 1.0 to 5.0 wt.%, preferably about 1.0 to 3.0 wt.%, and more preferably about 1.0 to 2.0 wt.%. In a preferred embodiment, dimethicone is employed in connection with at least one skin conditioning agent. The concentration of dimethicone in the formulation may be up to about 5.0 wt.%, preferably about 0.5 to 3.0 wt.% and more preferably about 1.0 to 2.0 wt.% of the lotion composition.

At least one conventional surfactants may be used in topical formulations to form the oil-in-water emulsion lotion of the present invention. For example, the surfactants may include, but are not limited to, polyoxyalkene oxides of C_{14}-C_{20} fatty alcohols and polyoxyalkylene sorbitan esters, or mixtures thereof. Preferred surfactants include CETOMACROGOL® 1000 (Crodor Inc.), CETETH-20®, TWEEN® 40 or BRIG® 78. The surfactant may be present in a concentration in the range of about 0.25 to 3.0 wt.%, preferably about 0.5 to 2.0 wt.%, and more preferably about 0.75 to 1.5 wt.%.

Optionally, mineral oil or white soft paraffin are incorporated into the lotion in relatively small amounts to act as a skin conditioner. The lotion may also be free of mineral oil and/or white soft paraffin or contain up to about 10.0 wt.%. The lotion may also contain up to about 5.0 wt.% or up to about 2.0 wt.% skin conditioner.

Propylene glycol may be present in the lotion formulation in a concentration of from about 5.0 to 15.0 wt.%, preferably about 7.0 to 12.0 wt.% and more preferably 9.0 to 11.0 wt.%.

The viscosity of the fluticasone lotion may be in the range of about 2,000 to 17,000 centipoise (cps), and preferably about 3,000 to 13,000 cps, as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

The pH range of the topical fluticasone lotion may be in the range of about 4 to 7. Conventional buffers may be employed in the lotion formulation to achieve the pH range. The buffers include, but are not limited to, sodium citrate/citric acid, dibasic sodium phosphate/citric acid, and the like.

Optionally, conventional preservatives may be used in the present invention. Preferably, preservatives employed in the formulation should pass US Pharmacopoeia, British Pharmacopoeia and European Pharmacopoeia standards. Preferred preservatives include, but are not limited to, imidurea, methylparaben, propylparaben and the like, and combinations thereof.

Treatment of skin conditions with the lotion of the present invention is accomplished by applying the lotion to the affected areas to be treated. The treatment regimen is varied

from patient to patient and condition to condition. In general, the fluticasone lotion is to be applied once or twice a day to a treatment area. Preferably, the lotion of the present invention is used to treat atopic dermatitis, inflammatory and pruritic manifestations and corticosteroid-responsive dermatoses.

The lotion of the present invention is manufactured in a conventional manner by mixing the ingredients at elevated temperatures (such as from 45-80°C) and then cooling the mixture to achieve a smooth, homogeneous oil-in-water emulsion.

The following examples merely illustrate the lotion compositions of the invention and are not to be construed as limiting the scope of the invention. Unless indicated otherwise, all weight percentages are based on the total weight of the composition.

EXAMPLES

Example 1

A topical 0.05 wt.% fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Cetostearyl alcohol, NF	5.00
Isopropyl myristate, NF	1.00
Dimethicone 360, NF	1.00
Cetomacrogol 1000, BP	1.00
Propylene glycol, USP	10.00
Imidurea, NF	0.30
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Citric acid (anhydrous), USP	0.05
Sodium citrate, USP	0.08
Purified water, USP	balance

Example 2

A topical 0.05 wt.% fluticasone propionate lotion formulation in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Cetostearyl alcohol, NF	5.25
Isopropyl myristate, NF	2.00
Propylene glycol, USP	0.00
Ceteth-20	0.75
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Citric Acid (anhydrous)	0.05
Dibasic sodium phosphate	0.06
Purified water, USP	balance

Example 3

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.0
Mineral Oil	3.0
Isopropyl myristate	3.0
Ceteth-20	0.75
Propylene Glycol	0.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 4

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.25
Mineral Oil	1.0
Isopropyl myristate	1.0
Ceteth-20	0.75
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 5

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	5.0
Mineral Oil	10.0
Isopropyl myristate	5.0
Ceteth-20	0.75
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Dibasic Sodium Phosphate	0.06
Imidurea	0.20
Water	balance

Example 6

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	2.5
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 7

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	5.0
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 8

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	6.0
Isopropyl myristate	2.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 9

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	4.7
Isopropyl myristate	3.75
Dimethicone	3.75
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 10

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	2.4
Isopropyl myristate	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 11

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.01
Stearyl Alcohol	5.0
Isopropyl myristate	3.0
Dimethicone	3.0
Ceteth-20	0.75
Propylene Glycol	5.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 12

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.01
Stearyl Alcohol	2.5
Mineral Oil	1.0
Isopropyl myristate	1.0
Dimethicone	1.0
Cetomacrogol 1000	0.5
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 13

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.1
Cetyl Alcohol	7.0
Mineral Oil	2.0
Isopropyl myristate	2.0
Dimethicone	2.0
Cetomacrogol 1000	1.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 14

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.1
Stearyl Alcohol	7.0
Mineral Oil	2.5
Dimethicone	2.5
Ceteth-20	1.0
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 15

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.1
Cetostearyl Alcohol	5.0
Mineral Oil	2.5
Dimethicone	1.0
Tween®40	0.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 16

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.1
Stearyl Alcohol	5.25
Mineral Oil	5.0
Brig®78	2.0
Propylene Glycol	5.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 17

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetyl Alcohol	2.0
Isopropyl myristate	5.0
Cetomacrogol 1000	0.5
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 18

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

Ingredient	(wt.%)
Fluticasone Propionate	0.05
Cetyl Alcohol	2.5
Dimethicone	5.0
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

The topical anti-inflammatory activity of fluticasone propionate formulations was measured using a vasoconstriction assay (McKenzie and Stoughton, Arch. Dermatol., 86, 608(1962)).

Approximately 0.1 mL of the drug product of Examples 1-18 were placed on a 2 cm^2 area of the volar aspect of each volunteer's forearm. Application sites were protected with a guard to prevent removal or smearing. The application sites were not occluded. After approximately 16 hours of contact, the protective guards were removed and the sites gently washed and dried.

Skin vasoconstrictor evaluations were preformed on a 4 point scale (0 [no blanching]-3[marked blanching]) at time points corresponding to 2, 3, 6, 8, and 24 hours after drug removal. The data were used to calculate the mean blanching response and the area under the curve (AUC) for the blanching versus time. The higher the score, mean or area under the curve (AUC), the more topically potent. The results are tabulated in Table 1.

Table 1

Measure*	Lotion Example 1	Lotion Example 2	CUTIVATE® (Fluticasone proprionate) Cream Comparative Example
AUC	28.4	26.7	21.4
Mean	1.58	1.49	1.22

*Results from 17 volunteers.

The fluticasone lotions of the present invention show higher vasoconstriction scores than fluticasone cream. As shown by the 17 patient data set, the vasoconstriction potency of the fluticasone lotions is greater than the cream.

The fluticasone lotion of the present invention has proven to be unexpectedly superior in terms of efficacy and safety. Evaluations were performed using the Vasoconstrictor Assay. Evaluations also used a human model to predict clinical potency of corticosteroids in (1) controlled efficacy and safety trials and (2) subjects with a corticosteroid-responsive dermatosis, atopic dermatitis. Safety and efficacy evaluations were performed on the fluticasone lotion 0.05% by applying the lotion extensively to all body regions: head and neck (including face), trunk, upper limbs and lower limbs.

The potency of the fluticasone lotion, as determined by the Vasoconstrictor Assay, was greater than mid-potency fluticasone cream (CUTIVATE™ Cream). The potency of the fluticasone lotion was less than the high-potency corticosteroid preparations. Application of the lotion formulation over 4 weeks resulted in a superior adverse event profile devoid of commonly encountered side effects encountered using corticosteroids in the mid-to-high potency range.

The instant fluticasone lotion was assessed in view of projected efficacy outcomes from the Vasoconstrictor Assay (VC Assay) in humans and corroborated by efficacy outcomes in multicenter vehicle-controlled clinical trials. It was highly desirable for the lotion formulation to show both systemic (adrenal axis suppression) and local (atrophogenic) responses to corticosteroids. The fluticasone lotion was unexpectedly

superior in both categories, and particularly superior in that no atrophy was observed (based on associated signs) even in the more susceptible region (i.e., the face, head and neck).

The Vasoconstrictor Assay (VC Assay; McKenzie and Stoughton) is a standard dermatological assay used to predict the potency of corticosteroid formulations. Potency is related to both side effect potential and efficacy in the treatment of mild to severe dermatoses. Reactions of particular concern include skin thinning (atrophy, including telangectasia), and adrenal axis suppression, which can occur more often (1) under occlusions or (2) when higher potency corticosteroids are employed.

In the VC assay, fluticasone lotion 0.05% was compared to low-potency (HYTONE™ Lotion), mid-potency (CUTIVATE™ Cream; and fluticasone cream 0.05%) and high-potency (TEMOVATE™ Cream; ELOCON™ Lotion). Potency was estimated for two subject populations (Intent to Treat and Positive responders) and includes 3 outcome assessments: 2-hour mean blanching score, are under the time-blanching score curve (AUC) and Average mean blanching from 5 timepoints. The results from the "responder" population is summarised in Table 2.

Table 2

Treatment	Potency	Responder Population		
		2 hour score	AUC	Avg. mean blanching
TEMOVATE™	High	2.7	36.6	2.0
ELOCON™	High	2.2	33.4	1.8
Fluticasone lotion (0.05%)	Mid to High	2.1	26.7	1.5
CUTIVATE™ Cream	Mid	1.8	21.4	1.2
HYTONE™ Lotion	Low	0.8	9.5	0.6

The results show that the fluticasone lotion of the present invention has an unexpectedly high potency for a lotion-based composition.

In addition, as shown in Table 3, criticality for the presence of fluticasone in the lotion of the present invention was established by the comparison between applying the vehicle alone (the fluticasone lotion minus the fluticasone propionate) and the fluticasone lotion. The FPL10005, FPL3003 and FPL30004 studies used the following fluticasone 0.05% lotion formulation.

Ingredient	(wt.%)
fluticasone propionate (micronized)	0.05
cetostearyl alcohol, NF	5.0
isopropyl myristate, NF	1.0
dimethicone 360, NF	1.0
polyoxyethylene (20) cetostearyl ether, NF	1.0
propylene glycol, USP	10.0
imidurea, NF	0.14
methylparaben, NF	0.17
propylparaben, NF	0.06
citric acid (hydrous), USP	0.05
sodium citrate, USP	0.08
purified water, USP	balance (also QSAD)

Table 3

Study	Diagnosis	Application	No. subjects	Outcome Good to cleared(%)
FPL30003	Atopic Dermatitis	QD for up to 4 weeks	FPL (110) Veh. (110)	FPL (78%)* Veh. (33%)
FPL30004	Atopic Dermatitis	QD for up to 4 weeks	FPL (111) Veh. (107)	FPL (68%)* Veh. (28%)

* subjects showing > 50% clearing of lesions

"Veh." is vehicle only formulation

The data of Table 3 show that the fluticasone lotion is more than twice as effective as the vehicle. In a once-a-day application, the differences (%) between the vehicle-only and the fluticasone lotion are 40% and 45% (FPL30004 and FPL30003, respectively). The advantage of the fluticasone propionate lotion over the vehicle control was unexpectedly superior. It is worth noting that the fluticasone lotion application rate was half the preferred application rate of twice per day.

Systemic safety of fluticasone lotion (study FPL10005) was assessed utilising the measurement of adrenal responsiveness to a challenge of cosyntropin ($ACTH_{1-29}$) and measuring the plasma levels of cortisol both before and 30 minutes after ACTH challenge. HPA axis was considered suppressed if the cortisol response to the challenge was less than 18 ug/dL. These studies were conducted in paediatric populations from 3 months to 5 years of age. Because children have a high ratio of body mass to surface, that population is considered to be more at risk than adults.

In these studies fluticasone formulations were tested following a 3 or 4 week course of twice daily application of the fluticasone lotion to at least 35% of the body surface area in subjects with moderate to severe eczema. The results are summarised in Table 4.

Table 4

Cortisol responses - plasma levels =18 ug/dL indicate suppression

Study	Preparation	Adrenal Responsiveness, #suppressed/total
FPL10005	Lotion	0 / 42

These data show that the fluticasone lotion did not suppress the adrenal responsiveness to ACTH stimulation. CUTIVATE™ lotion produced low adrenal suppression as evaluated by the cosyntropin ($ACTH_{1-29}$) stimulation test in paediatric subjects. This age group would be expected to be the most susceptible to side effects of corticosteroids. No adrenal suppression was noted for CUTIVATE™ lotion. These results were unexpectedly superior based on potency estimates from the VC Assay.

Treating skin diseases with topical corticosteroids is of particular concern where the skin is thin (e.g., the face) due to the potential atrophy side effect. Skin atrophy and atrophy-associated signs (such as telangectasia) were monitored in safety studies (HPA Axis Suppression) and efficacy (multicenter pivotal trials). The fluticasone lotion showed no atrophy-associated changes (see Table 4). In addition, atrophogenic potential was assessed in two large multicenter trials (FPL30003, N= 110 treated with fluticasone); FPL30004; N= 111 treated with fluticasone). The subjects had moderate-to-severe atopic dermatitis. After once daily administration for up to 4 weeks, no atrophy or associated signs were ascribed to drug treatment.

Based on the observed outcomes in the VC Assay (used to predict clinical potency), it was expected (1) that the therapeutic benefit would be only slightly more than that for CUTIVATE™ Cream and (2) that the side effects would reflect those observed for CUTIVATE™ Cream. The results were unexpected in that the lotion formulation was more effective than, and superior to, the cream. At half the application rate of fluticasone lotion, a lack of side effects were observed. That observation was unexpected since application of steroids of similar potency typically cause some side effects. As noted herein for the lotion, the lack of both systemic (HPA Axis suppression) and local side effects, even to sensitive areas such as the face (head and neck region) was unexpected.

It will be apparent to those skilled in the art that many modifications and equivalents thereof may be made without departing from the spirit and scope of the invention as set forth in the appended claims.

We claim:

1. A topical lotion comprising:
about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;
about 1.0 to 10.0 wt.% of a C_{14}-C_{20} fatty alcohol or mixtures thereof;
about 1.0 to 5.0 wt.% of at least one skin conditioning agent;
about 5.0 to 15.0 wt.% propylene glycol;
up to about 10.0 wt.% mineral oil or white soft paraffin; and
the balance in water.

2. A topical lotion comprising:
about 0.005 to 1.0 wt.% fluticasone propionate;
about 3.0 to 7.0 wt.% of a C_{14}-C_{20} fatty alcohol, or mixtures thereof;
about 0.5 to 3.0 wt.% of at least one skin conditioning agent;
about 0.25 to 2.0 wt.% of at least one surfactant;
about 7.0 to 12.0 wt.% propylene glycol;
up to about 10 wt.% of mineral oil or white soft paraffin; and
the balance in water.

3. The lotion according to claim 1, further comprising less than about 5.0 wt.% dimethicone.

4. The lotion according to claim 2, further comprising less than about 5.0 wt.% dimethicone.

5. The lotion according to claim 1, wherein said pharmaceutically acceptable ester of fluticasone is fluticasone propionate.

6. The lotion according to claim 1, comprising:
about 0.05 wt.% fluticasone propionate,
about 5.0 wt.% cetostearyl alcohol,
about 1.0 wt.% isopropyl myristate,
about 1.0 wt.% dimethicone,
about 1.0 wt.% cetomacrogol,

about 10.0 wt.% propylene glycol
less than about 0.30 wt.% imidurea,
less than about 0.20 wt.% methyl paraben,
less than about 0.10 wt.% propyl paraben,
about 0.05 wt.% citric acid (anhydrous),
about 0.08 wt.% sodium citrate, and
the balance in purified water.

7. The lotion according to claim 1, comprising:
about 0.05 wt.% fluticasone propionate,
about 5.25 wt.% cetostearyl alcohol,
about 2.0 wt.% isopropyl myristate,
about 10.0 wt.% propylene glycol,
about 0.20 wt.% imidurea,
about 0.20 wt.% methyl paraben,
about 0.10 wt.% propyl paraben, and
the balance in purified water.

8. The lotion according to claim 1, having a viscosity of about 2,000 to 17,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

9. The lotion according to claim 2, having the formula
about 5.25 wt.% cetostearyl alcohol,
about 2.0 wt.% isopropyl myristate,
about 10.0 wt.% propylene glycol,
about 0.20 wt.% imidurea,
about 0.20 wt.% methyl paraben,
about 0.10 wt.% propyl paraben, and
the balance in purified water.

10. The lotion according to claim 1, having a viscosity of from about 3,000 to 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C

11. The lotion according to claim 2, having a viscosity of from about 3,000 to 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

12. The lotion according to claim 1, free of mineral oil or white soft paraffin.

13. The lotion according to claim 2, free of mineral oil or white soft paraffin.

14. Use of the lotion according to claim 1 to increase the vasoconstrictor potency of fluticasone.

15. Use of the lotion according to claim 2 to increase the vasoconstrictor potency of fluticasone proprionate.

16. A process for preparing a lotion according to claim 1, comprising:
mixing the ingredients recited in claim 1 at an elevated temperature; and
cooling said mixture.

17. A process for preparing a lotion according to claim 1, comprising:
mixing the ingredients recited in claim 1 at an elevated temperature; and
heating said mixture.

18. A topical lotion comprising:
about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;
a thickening effective concentration of at least one thickener;
a conditioning effective concentration of at least one skin conditioning agent;
an emulsifying effective amount of a surfactant, and
the balance in water.

19. The lotion of claim 18, wherein the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5.

20. The lotion of claim 18, wherein the lotion is chemically and physically stable for at least 6 months at 40°C.

21. A method of treating a skin condition comprising:
providing a lotion including about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to about 10.0 wt.% of a C_{14}-C_{20} fatty alcohol or mixtures thereof; about 1.0 to about 5.0 wt.% of at least one skin conditioning agents; about 5.0 to about 15.0 wt.% of propylene glycol; less than about 10.0 wt.% of mineral oil or white soft paraffin, and the balance in water; and,
applying the lotion to the skin having the skin condition.

22. The method of claim 21, wherein the skin condition is corticosteroid-responsive dermatosis, atopic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting or pruritis.

23. The topical lotion of claim 21, wherein the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5.

24. The lotion of claim 21, wherein the lotion is chemically and physically stable for at least 6 months at 40°C.

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3	FULL NAME OF INVENTOR	FAMILY NAME: **KELLY**	FIRST GIVEN NAME: **Frances**	SECOND GIVEN NAME/INITIAL: **Furr**
	INVENTOR'S SIGNATURE	Frances Furr Kelly		X April 18, 2001
0	RESIDENCE & CITIZENSHIP	CITY: **Durham**	STATE OR FOREIGN COUNTRY: **NC**	COUNTRY OF CITIZENSHIP: **US**
3	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive, PO Box 13398**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **NC 27709, US**

COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued				ATTORNEY'S DOCKET NUMBER PU3556USW
	FULL NAME OF INVENTOR	FAMILY NAME **LATHROP**	FIRST GIVEN NAME **Robert**	SECOND GIVEN NAME/INITIAL **William**
	INVENTOR'S SIGNATURE	X Lathrop	Robert	X William 4/6/2001
0	RESIDENCE & CITIZENSHIP	CITY **Fort Collins**	STATE OR FOREIGN COUNTRY **CO**	COUNTRY OF CITIZENSHIP **US**
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS **GlaxoSmithKline Five Moore Drive, PO Box 13398**	CITY **Research Triangle Park**	STATE & ZIP CODE/COUNTRY **NC 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME **RAJAGOPALAN**	FIRST GIVEN NAME **Rukmini**	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY **Durham**	STATE OR FOREIGN COUNTRY **NC**	COUNTRY OF CITIZENSHIP **US**
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS **GlaxoSmithKline Five Moore Drive, PO Box 13398**	CITY **Research Triangle Park**	STATE & ZIP CODE/COUNTRY **NC 27709, US**

COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued				ATTORNEY'S DOCKET NUMBER PU3556USW
2	FULL NAME OF INVENTOR	FAMILY NAME **LATHROP**	FIRST GIVEN NAME **Robert**	SECOND GIVEN NAME/INITIAL **William**
	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY **Fort Collins**	STATE OR FOREIGN COUNTRY **CO**	COUNTRY OF CITIZENSHIP **US**
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS **GlaxoSmithKline** **Five Moore Drive, PO Box 13398**	CITY **Research Triangle Park**	STATE & ZIP CODE/COUNTRY **NC 27709, US**
5	FULL NAME OF INVENTOR	FAMILY NAME **RAJAGOPALAN**	FIRST GIVEN NAME **Rukmini**	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	R Rajagopalan		10APR2001
0	RESIDENCE & CITIZENSHIP	CITY **Durham**	STATE OR FOREIGN COUNTRY **NC**	COUNTRY OF CITIZENSHIP **US**
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS **GlaxoSmithKline** **Five Moore Drive, PO Box 13398**	CITY **Research Triangle Park**	STATE & ZIP CODE/COUNTRY **NC 27709, US**

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY

ATTORNEY'S DOCKET
PU3556USW
First Names Inventor: **Gordon J. DOW**
Complete if known: App No.:
Filing Date
Group Art Unit:

(X) Declaration submitted with initial filing or

( )Declaration submitted after initial filing (surcharge required 37CFR1.16(e))

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

the specification of which (check only one item below):

[ ]is attached hereto.

OR

[x] was filed on **20 October 1999** as United States application Serial No. _____ or **PCT** International

Application Number **PCT/GB99/03472** filed and was amended on (MM/DD/YYYY) _____(if applicable)

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PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

Prior Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY))	PRIORITY CLAIMED
1. 9823036.0	GB	22 October 1998	X
2.			
3.			
4.			
5.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date (MM/DD/YYYY)	
1.		
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4.		
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COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued				ATTORNEY'S DOCKET NUMBER PU3556USW
2	FULL NAME OF INVENTOR	FAMILY NAME **LATHROP**	FIRST GIVEN NAME **Robert**	SECOND GIVEN NAME/INITIAL **William**
	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY **Fort Collins**	STATE OR FOREIGN COUNTRY **CO**	COUNTRY OF CITIZENSHIP **US**
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS **GlaxoSmithKline** **Five Moore Drive, PO Box 13398**	CITY **Research Triangle Park**	STATE & ZIP CODE/COUNTRY **NC 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME **RAJAGOPALAN**	FIRST GIVEN NAME **Rukmini**	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY **Durham**	STATE OR FOREIGN COUNTRY **NC**	COUNTRY OF CITIZENSHIP **US**
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ATTORNEY'S DOCKET
PU3556USW
First Names Inventor: **Gordon J. DOW**
Complete if known: App No.:
Filing Date
Group Art Unit:

(X) Declaration submitted with initial filing or

( )Declaration submitted after initial filing (surcharge required 37CFR1.16(e))

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FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

the specification of which (check only one item below):

[ ]is attached hereto.

OR

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Application Number **PCT/GB99/03472** filed and was amended on (MM/DD/YYYY) _____(if applicable)

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COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued				ATTORNEY'S DOCKET NUMBER PU3556USW
2	FULL NAME OF INVENTOR	FAMILY NAME **LATHROP**	FIRST GIVEN NAME **Robert**	SECOND GIVEN NAME/INITIAL **William**
	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY **Fort Collins**	STATE OR FOREIGN COUNTRY **CO**	COUNTRY OF CITIZENSHIP **US**
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS **GlaxoSmithKline** **Five Moore Drive, PO Box 13398**	CITY **Research Triangle Park**	STATE & ZIP CODE/COUNTRY **NC 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME **RAJAGOPALAN**	FIRST GIVEN NAME **Rukmini**	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY **Durham**	STATE OR FOREIGN COUNTRY **NC**	COUNTRY OF CITIZENSHIP **US**
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS **GlaxoSmithKline** **Five Moore Drive, PO Box 13398**	CITY **Research Triangle Park**	STATE & ZIP CODE/COUNTRY **NC 27709, US**

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY

ATTORNEY'S DOCKET
PU3556USW
First Names Inventor: **Gordon J. DOW**
Complete if known: App No.:
Filing Date
Group Art Unit:

(X) Declaration submitted with initial filing or

( )Declaration submitted after initial filing (surcharge required 37CFR1.16(e))

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the specification of which (check only one item below):

[ ]is attached hereto.

OR

[x] was filed on **20 October 1999** as United States application Serial No. _____ or **PCT** International

Application Number **PCT/GB99/03472** filed and was amended on (MM/DD/YYYY) _____(if applicable)

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COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued				ATTORNEY'S DOCKET NUMBER PU3556USW
2	FULL NAME OF INVENTOR	FAMILY NAME **LATHROP**	FIRST GIVEN NAME **Robert**	SECOND GIVEN NAME/INITIAL **William**
	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY **Fort Collins**	STATE OR FOREIGN COUNTRY **CO**	COUNTRY OF CITIZENSHIP **US**
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS **GlaxoSmithKline** **Five Moore Drive, PO Box 13398**	CITY **Research Triangle Park**	STATE & ZIP CODE/COUNTRY **NC 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME **RAJAGOPALAN**	FIRST GIVEN NAME **Rukmini**	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY **Durham**	STATE OR FOREIGN COUNTRY **NC**	COUNTRY OF CITIZENSHIP **US**
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS **GlaxoSmithKline** **Five Moore Drive, PO Box 13398**	CITY **Research Triangle Park**	STATE & ZIP CODE/COUNTRY **NC 27709, US**

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY

ATTORNEY'S DOCKET
PU3556USW
First Names Inventor. **Gordon J. DOW**
Complete if known: App No.:
Filing Date
Group Art Unit:

(X) Declaration submitted with initial filing or

( )Declaration submitted after initial filing (surcharge required 37CFR1.16(e))

As below named inventor. I hereby declare that:

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FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

the specification of which (check only one item below):

[ ]is attached hereto.

OR

[x] was filed on **20 October 1999** as United States application Serial No. _____ or **PCT** International

Application Number **PCT/GB99/03472** filed and was amended on (MM/DD/YYYY) _____(if applicable)

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PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

Prior Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY))	PRIORITY CLAIMED
1. 9823036.0	GB	22 October 1998	X
2.			
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I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date (MM/DD/YYYY)	
1.		
2.		
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COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued

ATTORNEY'S DOCKET NUMBER: PU3556USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one) PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith. (List name and registration number)

David J. Levy	Reg. No. 27,655	James P. Riek	Reg. No. 39,009	Bonnie L. Deppenbrock	Reg. No. 28,209
Charles E. Dadswell	Reg. No. 35,851	Virginia C. Bennett	Reg. No. 37,092	John L. Lemanowicz	Reg. No. 37,386
Karen L. Prus	Reg. No. 39,337	Frank P.Grassler	Reg. No. 31,164		
Robert H. Brink	Reg. No. 36,094	Christopher P. Rogers	Reg. No. 36,334		
Elizabeth Selby	Reg. No. 38,298	Lorie Ann Morgan	Reg. No. 38,181		

Send Correspondence to:
David J. Levy, Patent Counsel
Global Intellectual Property Department
Glaxo Wellcome Inc.
Five Moore Drive, PO Box 13398
Research Triangle Park, NC 27709

23347
PATENT TRADEMARK OFFICE

Direct Telephone Calls to:
Christopher P. Rogers
919-483-1240

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2	FULL NAME OF INVENTOR	FAMILY NAME: **DOW**	FIRST GIVEN NAME: **Gordon**	SECOND GIVEN NAME/INITIAL: **J.**
	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY: **Petaluma**	STATE OR FOREIGN COUNTRY: **CA**	COUNTRY OF CITIZENSHIP: **US**
1	POST OFFICE ADDRESS	*POST OFFICE ADDRESS: **Dow Pharmaceutical Science 1330A Redwoodway**	CITY: **Petaluma**	STATE & ZIP CODE/COUNTRY: **CA 94954, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **JOHNSON**	FIRST GIVEN NAME: **Keith**	SECOND GIVEN NAME/INITIAL: **Arthur**
	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY: **Durham**	STATE OR FOREIGN COUNTRY: **NC**	COUNTRY OF CITIZENSHIP: **US**
2	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **GlaxoSmithKline Five Moore Drive, PO Box 13398**	CITY: **Research Triangle Park**	STATE & ZIP CODE/COUNTRY: **NC 27709, US**
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	INVENTOR'S SIGNATURE			
0	RESIDENCE & CITIZENSHIP	CITY: **Durham**	STATE OR FOREIGN COUNTRY: **NC**	COUNTRY OF CITIZENSHIP: **US**
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COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY

ATTORNEY'S DOCKET
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First Names Inventor: **Gordon J. DOW**
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OR
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2	FULL NAME OF INVENTOR	FAMILY NAME: **DOW**	FIRST GIVEN NAME: **Gordon**		SECOND GIVEN NAME/INITIAL: **J.**
	INVENTOR'S SIGNATURE				
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